

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Before the Board of Patent Appeals and Interferences

BRIEF FOR THE APPELLANTS

Ex parte Guthrie et al.

Serial Number: 09/528,488

Filed: March 17, 2000

Appeal No.:

Group Art Unit: 1623

Examiner: Howard V. Owens

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Docket No. 0146.98

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PATENT APPLICATION

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re application of
Applicant: Najla Guthrie et al.

Title: Compositions and Methods of Treating, Reducing,
and Preventing Cardiovascular Diseases and Disorders
with Polymethoxyflavones

Serial No.: 09/528,488

Group Art Unit: 1623

Examiner: Howard V. Owens

Docket No.: 52953.8

Filed: March 17, 2000

APPEAL BRIEF

Honorable Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

1) Real Party In Interest

The real party in interest is the United States of America
as represented by the Secretary of Agriculture, Washington, D.C.;
and KGK Synergize, INC.

2) Related Appeals and Interferences

There are no related appeals and interferences.

3) Status of Claims

Claims 1-12 were originally filed in this application. Claims 1-12 were canceled by amendment and new claims 13-22 were added by amendment. Claims 13, 15, 16, 18-22 were canceled by amendment and new claims 23-28 were added in an amendment after final rejection.

The new claims were entered in an advisory action with a mail date of September 9, 2003. Claims 14, 17, and 23-28 are currently pending and are a part of this appeal.

4) Status of Amendments After Final Rejection

A response canceling claims 13, 15-16, and 18-22 and adding claims 23-28 was filed on August 20, 2003. The amendment was entered by filing the Notice of Appeal dated August 20, 2003 as authorized in the advisory action dated September 09, 2003 which maintained the rejection under 35 USC 103(a) in the final Office action.

5) Summary of Invention

The invention is directed to compositions and methods for reducing apolipoprotein B production using novel compositions containing a polymethoxyflavone or mixtures of polymethoxyflavones in amounts to reduce the amount of apolipoprotein B which contribute to cardiovascular diseases or disorders. Humans with coronary heart disease have higher levels of Apolipoprotein B and Apolipoprotein B concentrations reflect the number of Low density lipoproteins (LDLs) and very low density lipoprotein (VLDL) particles in arteries. A polymethoxyflavone is a flavone substituted with methoxy groups. The compositions and methods of using the compositions include the following polymethoxyflavones alone or in mixtures in amounts to reduce levels of apolipoprotein B: limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethyl ether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, sinensetin (5,6,7,3',4'-pentamethoxyflavone), tetra-O-methyl-scutellarein, 5-desmethylsinensetin (5-hydroxy-3,7,3',4'-

tetramethoxyflavone), , 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-O-methylisoscutellarein (5,7,8,4'-tetramethoxyflavone), quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethylether-3-acetate, quercetin tetramethylether (5-hydroxy-3,7,3',4'-tetramethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyl ether, and 5,7,3'4'-tetramethylether (3-hydroxy-5,7,3',4'-tetramethoxyflavone).

6) Issues

Issue 1-Whether the Guthrie et al. published patent application US2001/0055627 renders the claimed invention obvious under 35 USC 103 (a) .

7) Grouping of the Claims

Claims 14,23,24, and 26, stand or fall together.
Claims 17, 25, 27, and 28 stand or fall together.

8) Arguments

(a) Claims 14,23,24, and 26 are patentable over the art of record. It is improper to reject the claims under 35 USC subsection 103(a) when the reference fails to render the claimed invention obvious.

Claims 14,23,24, and 26 were finally rejected under 35 USC 103(a) as being unpatentable over Guthrie et al., published U.S. Patent Application US2001/0055627.

The Invention of claims 14,23,24, and 26 is directed to a method of reducing apolipoprotein B production that includes the steps of:

providing an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone),

limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethylether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, and mixtures thereof. (Claim 14)

providing an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of sinensetin, tetra-O-methyl-scutellarein, 5-desmethylsinensetin and mixtures thereof. (Claim 23)

providing an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-O-methylisoscutellarein (5,7,8,4'-tetramethoxyflavone), sinensetin (5,6,7,3',4'-pentamethoxyflavone), 5-desmethylsinensetin (5-hydroxy-6,7,3',4'-pentamethoxyflavone), quercetin tetramethylether (5-hydroxy-3,7,3',4'-pentamethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyl ether, quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethylether-3-acetate, 5,7,3',4'-tetramethylether (3 hydroxy-5,7,3',4'-tetramethoxyflavone) and mixtures thereof. (Claim 24)

providing an apolipoprotein B reducing amount of a polymethoxyflavone wherein said polymethoxyflavone is 5-desmethylsinensetin. (Claim 26)

Although the final rejection states that the Guthrie et al.

published patent application US2001/0055627 renders the claimed invention on appeal *prima facie* obvious, the reference fails to teach the instantly claimed invention and fails to provide motivation one of ordinary skill in the art at the time the claimed invention was made. Therefore Guthrie et al. fails to render the claimed invention *prima facie* obvious.

The Guthrie et al published patent application teaches compositions and methods for the prevention and treatment of atherosclerosis, hyperlipidemia, and hypercholesterolemia with limonoids, flavonoids and/or tocotrienols. Furthermore, the published application teaches that citrus limonoids, flavonoids, and/or tocotrienols in **specific combinations** (emphasis added) are used to inhibit production of cholesterol, low density lipoproteins (LDL) and apo-B protein (See specifically paragraph [0002]). No where does the reference teach or suggest that any or all of these compounds exhibit this activity. Specifically, the published patent application states that naringenin and hesperitin at high levels in citrus fruits have the ability to reduce overall production of apo-B in HepG2 cells (See paragraph [0054] and Figure 3a and b). The published application further teaches that limonin and nomilin induced a substantial or moderate reduction of apo-B levels in HepG2 cells (See paragraph [0056]). In paragraph [0057], the published application states further that tangeretin and nobletin also reduce apo-B production.

The claimed invention on appeal teaches the use of

apolipoprotein reducing amounts of a polymethoxyflavone that includes limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethylether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,5,7,4'-tetraethylether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, sinensetin, tetra-O-methyl-scutellarein, 5-desmethylsinensetin, 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-O-methylicoscutellarein (5,7,8,4'-tetramethoxyflavone), sinensetin (5,6,7,3',4'-pentamethoxyflavone), 5-desmethylsinensetin (5-hydroxy-6,7,3',4'-tetramethoxyflavone), quercetin tetramethylether (5-hydroxy-3,7,3',4'-tetramethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyl ether, quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethylether-3-acetate, 5,7,3',4'-tetramethylether (3 hydroxy-5,7,3',4'-tetramethoxyflavone), and mixtures thereof.

Guthrie et al published patent application:

(1) fails to teach the specifically claimed polymethoxyflavones in a method for reducing levels of apolipoprotein B which is specifically pointed out by the Office in the final rejection with a mail date of May 20, 2003, on page 2, paragraph 4, lines 7-8, and

(2) the published patent application fails to teach the class of

flavone/flavonoids broadly as agents effective in reducing apo-B.

No other references have been provided to cure these deficiencies of Guthrie et al. The Office is using the improper standard of obvious to try. It is respectfully submitted that the essence of obviousness does not arise by merely picking and choosing from the prior art to produce the claimed invention. "In order to establish *prima facie* obviousness it is necessary for the examiner to present evidence preferably in the form of some teaching, suggestion, incentive, or general available knowledge, that one of ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (Bd. Pat. & Int'l, 1993). Starting from this correct standard of obviousness, the error of the Office is clear-the rejection is improper because the Office has failed to identify any teachings in the prior art motivating one of ordinary skill in the art at the time the claimed invention was made to produce the methods of the presently claimed invention. No references or combination of references have been provided which teach, suggest, or motivate one of ordinary skill in the art to modify the Guthrie et al. application to used the polymethoxyflavones of the instantly claimed invention to reduce apolipoprotein B production. There is simply no motivation save for the teachings of the inventors application to produce the claimed invention. The Office is also using the improper standard of **IMPROPER**

hindsight analysis. It is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. One cannot use improper hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. The Guthrie et al. application fails to render the instantly claimed invention *prima facie* obvious.

The rejection is improper.

(b) Claims 17, 25, 27, and 28 are patentable over the art of record. It is improper to reject the claims under 35 USC subsection 103(a) when the reference fails to render the claimed invention obvious.

Claims 17, 25, 27, and 28 were finally rejected under 35 USC 103(a) as being unpatentable over Guthrie et al., published U.S. Patent Application US2001/0055627. The invention of claims 17, 25, 27, and 28 is directed to compositions for reducing apolipoprotein B production that include:

an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethyl ether (8,3-

dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, and mixtures thereof. (Claim 17)

an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of sinensetin, tetra-O-methylscutellarein, 5-desmethylsinensetin and mixtures thereof. (Claim 25)

an apolipoprotein B reducing amount of a polymethoxyflavone wherein said polymethoxyflavone is 5-desmethylsinensetin. (Claim 27)

an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-O-methylisoscutellarein (5,7,8,4'-tetramethoxyflavone), sinensetin (5,6,7,3',4'-pentamethoxyflavone), 5-desmethylsinensetin (5-hydroxy-6,7,3',4'-tetramethoxyflavone), quercetin tetramethylether (5-hydroxy-3,7,3',4'-tetramethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyloether, quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethylether-3-acetate, 5,7,3',4'-tetramethylether (3 hydroxy-5,7,3',4'-tetramethoxyflavone) and mixtures thereof. (Claim 28)

Although the final rejection states that the Guthrie et al. published patent application US2001/0055627 renders the claimed invention on appeal *prima facie* obvious, the reference fails to teach the instantly claimed invention and fails to provide motivation one of ordinary skill in the art at the time the claimed invention was made.

Therefore Guthrie et al. fails to render the claimed invention *prima facie* obvious.

The Guthrie et al published patent application teaches compositions and methods for the prevention and treatment of atherosclerosis, hyperlipidemia, and hypercholesterolemia with limonoids, flavonoids and/or tocotrienols. Furthermore, the published application teaches that citrus limonoids, flavonoids, and/or tocotrienols in **specific combinations** (emphasis added) are used to inhibit production of cholesterol, low density lipoproteins (LDL) and apo-B protein (See specifically paragraph [0002]). No where does the reference teach or suggest that any or all of these compounds exhibit this activity. Specifically, the published patent application states that naringenin and hesperitin at high levels in citrus fruits have the ability to reduce overall production of apo-B in HepG2 cells (See paragraph [0054] and Figure 3a and b). The published application further teaches that limonin and nomilin induced a substantial or moderate reduction of apo-B levels in HepG2 cells (See paragraph [0056]). In paragraph [0057], the published application states further that tangeretin and nobletin also reduce apo-B production.

The claimed invention on appeal teaches compositions comprising apolipoprotein reducing amounts of a polymethoxyflavone that includes limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether

(5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethylether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, sinensetin, tetra-O-methyl-scutellarein, 5-desmethylsinensetin, 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-O-methyisoscutellarein (5,7,8,4'-tetramethoxyflavone), sinensetin (5,6,7,3',4'-pentamethoxyflavone), 5-desmethylsinensetin (5-hydroxy-6,7,3',4'-tetramethoxyflavone), quercetin tetramethylether (5-hydroxy-3,7,3',4'-tetramethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyl ether, quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethylether-3-acetate, 5,7,3',4'-tetramethylether (3 hydroxy-5,7,3',4'-tetramethoxyflavone), and mixtures thereof.

Guthrie et al published patent application:

(1) fails to teach the specifically claimed polymethoxyflavones in compositions for reducing levels of apolipoprotein B which is specifically pointed out by the Office in the final rejection with a mail date of May 20, 2003, on page 2, paragraph 4, lines 7-8, and

(2) the published patent application fails to teach the class of flavone/flavonoids broadly as agents effective in reducing apo-B.

No other references have been provided to cure these deficiencies of Guthrie et al. The Office is using the improper standard of obvious to try. It is respectfully submitted that the essence of

obviousness does not arise by merely picking and choosing from the prior art to produce the claimed invention. "In order to establish *prima facie* obviousness it is necessary for the examiner to present evidence preferably in the form of some teaching, suggestion, incentive, or general available knowledge, that one of ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (Bd. Pat. & Int'l, 1993). Starting from this correct standard of obviousness, the error of the Office is clear-the rejection is improper because the Office has failed to identify any teachings in the prior art motivating one of ordinary skill in the art at the time the claimed invention was made to produce the methods of the presently claimed invention. No references or combination of references have been provided which teach, suggest, or motivate one of ordinary skill in the art to modify the Guthrie et al. application to use the polymethoxyflavones of the instantly claimed invention in compositions for reducing apolipoprotein B production. There is simply no motivation save for the teachings of the inventors application to produce the claimed invention. The Office is also using the improper standard of **IMPROPER** hindsight analysis. It is impermissible to use the claimed invention as an instruction manual or template to piece together the teachings of the prior art so that the claimed invention is rendered obvious. One cannot use improper hindsight reconstruction

to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. The Guthrie et al. application fails to render the instantly claimed invention *prima facie* obvious.

The rejection is improper.

9) Conclusion

In view of the fact that the reference fails to render the instantly claimed invention *prima facie* obvious, Appellants respectfully request this Board to reverse the final rejection in due course.

Respectfully submitted,

October 23, 2003

Gail Poulo

Date

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APPENDIX**10) Claims on Appeal**

14. A method for reducing apolipoprotein B production comprising providing an apolipoprotein reducing amount of a polymethoxyflavone selected from the group consisting of limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethylether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, and mixtures thereof.

17. A composition for reducing apolipoprotein B production comprising an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of limocitrin-3,7,4'-trimethylether (5-hydroxy-3,7,8,3',4'-pentamethoxyflavone), limocitrin-3,5,7,4'-tetramethylether (5-hydroxy-3,7,8,3',4'-hexamethoxyflavone), limocitrin-3,5,7,4'-tetraethylether (8,3-dimethoxy-3,5,7,4'-tetraethoxyflavone), limocitrin-3,7,4'-trimethylether-5-acetate, and mixtures thereof.

23. A method for reducing apolipoprotein B production comprising providing an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of sinensetin, tetra-O-methyl-scutellarein, 5-desmethylsinensetin and mixtures thereof.

24. A method for reducing apolipoprotein B production comprising providing an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-

O-methylisoscutellarein (5,7,8,4'-tetramethoxyflavone), sinensetin (5,6,7,3',4'-(pentamethoxyflavone), 5-desmethylsinensetin (5-hydroxy-6,7,3',4'-tetramethoxyflavone), quercetin tetramethylether (5-hydroxy-3,7,3',4'-tetramethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyl ether, quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethyl ether-3-acetate, 5,7,3',4'-tetramethylether (3-hydroxy-5,7,3',4'-tetramethoxyflavone), and mixtures thereof.

25. A composition for reducing apolipoprotein B production comprising an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of sinensetin, tetra-O-methyl-scutellarein, 5-desmethylsinensetin, and mixtures thereof.

26. The method of claim 23 wherein said polymethoxyflavone is 5-desmethylsinensetin.

27. The composition of claim 25 wherein said polymethoxyflavone is 5-desmethylsinensetin.

28. A composition for reducing apolipoprotein B production comprising an apolipoprotein B reducing amount of a polymethoxyflavone selected from the group consisting of 5-desmethylnobiletin (5-hydroxy-7,7,8,3',4'-pentamethoxyflavone), tetra-O-methylisoscutellarein (5,7,8,4'-tetramethoxyflavone), sinensetin (5,6,7,3',4'-pentamethoxyflavone), 5-desmethylsinensetin (5-hydroxy-6,7,3',4'-tetramethoxyflavone), quercetin tetramethylether (5-hydroxy-3,7,3',4'-tetramethoxyflavone), quercetin-3,5-dimethylether-7,3',4'-tribenzyl ether, quercetin pentamethylether (3,5,7,3',4'-pentamethoxyflavone), quercetin-5,7,3',4'-tetramethyl ether-3-acetate, 5,7,3',4'-tetramethyl ether (3-hydroxy-5,7,3',4'-tetramethoxyflavone),

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and mixtures thereof.